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The Impact of Patient and Lesion Complexity on Clinical and Angiographic Outcomes After Revascularization With Zotarolimus- and Everolimus-Eluting Stents

A Substudy of the RESOLUTE All Comers Trial (A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention)

Giulio G. Stefanini, MD,* Patrick W. Serruys, MD, PhD,† Sigmund Silber, MD, PhD,‡ Ahmed A. Khattab, MD,* Robert J. van Geuns, MD, PhD,† Gert Richardt, MD,§ Pawel E. Buszman, MD, PhD,‖ Henning Kelbæk, MD,¶ Adrianus J. van Boven, MD, PhD,# Sjoerd H. Hofma, MD, PhD,# Axel Linke, MD, PhD,** Volker Klauss, MD, PhD,†† William Wijns, MD, PhD,‡‡ Carlos Macaya, MD, PhD,§§ Philippe Garot, MD,‖‖ Carlo Di Mario, MD, PhD,¶¶ Ganesh Manoharan, MBBCh, MD,## Ran Kornowski, MD,*** Thomas Ischinger, MD, PhD,††† Antonio L. Bartorelli, MD,‡‡‡ Pierre Gobbens, BSc,§§§ Stephan Windecker, MD*

Bern, Switzerland; Rotterdam and Leeuwarden, the Netherlands; Munich, Bad Segeberg, and Leipzig, Germany; Katowice, Poland; Copenhagen, Denmark; Aalst, Belgium; Madrid, Spain; Quincy, France; London and Belfast, United Kingdom; Tel Aviv, Israel; and Milan, Italy

Objectives The aim of this study was to investigate the impact of patient and lesion complexity on outcomes with newer-generation zotarolimus-eluting stents (ZES) and everolimus-eluting stents (EES).

Background Clinical and angiographic outcomes of newer-generation stents have not been described among complex patients.

Methods Patients enrolled in the RESOLUTE All Comers trial (A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention) were stratified into "complex" and "simple."

Results Of 2,292 patients, 1,520 (66.3%) were complex and treated with ZES (n = 764) or EES (n = 756). Event rates were higher among complex patients, and results did not differ between ZES and EES, regardless of complexity. At 1 year, target lesion failure was 8.9% in ZES- and 9.7% in EES-treated complex patients (p = 0.66) and 6.8% in ZES- and 5.7% in EES-treated simple patients (p = 0.55). Rates of cardiac death (1.3% vs. 2.2%, p = 0.24), target-vessel myocardial infarction (4.3% vs. 4.4%, p = 0.90), and clinically indicated target lesion revascularization (4.4% vs. 4.0%, p = 0.80) were similar for both stent types among complex patients. Definite or probable stent thrombosis occurred in 20 (1.3%) complex patients with no difference between ZES (1.7%) and EES (0.9%, p = 0.26). Angiographic follow-up showed similar results for ZES and EES in terms of in-stent percentage diameter stenosis (22.2 ± 15.4% vs. 21.4 ± 15.8%, p = 0.67) and in-segment binary restenosis (6.6% vs. 8.0%, p = 0.82) in the complex group.

Conclusions In this all-comers randomized trial, major adverse cardiovascular events were more frequent among complex than simple patients. The newer-generation ZES and EES proved to be safe and effective, regardless of complexity, with similar clinical and angiographic outcomes for both stent types through 1 year. (RESOLUTE-III All Comers Trial: A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention; NCT00617084) (J Am Coll Cardiol 2011;57:2221–32) © 2011 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

BMS = bare-metal stent(s)
CI = confidence interval
DES = drug-eluting stent(s)
ECG = electrocardiogram/electrocardiographic
EES = everolimus-eluting stent(s)
MI = myocardial infarction
ST = stent thrombosis
TLF = target lesion failure
TLR = target lesion revascularization
ZES = zotarolimus-eluting stent(s)

Drug-eluting stents (DES) are currently used in complex patient and lesion subsets in 60% to 70% of cases (1,2). However, in light of data available from randomized trials (3–5), the U.S. Food and Drug Administration on-label indication is limited to low-risk patients with stable coronary artery disease and simple single, de novo lesions. Concerns regarding off-label use of DES were raised mainly due to the observation of higher rates of stent thrombosis (ST) associated with the unrestricted use of DES (6) and its potential to offset DES efficacy among more complex patients treated outside randomized clinical trials. Several studies and 1 meta-analysis with special focus on DES safety showed less favorable outcomes of patients with off-label compared with on-label indications with both DES and bare-metal stents (BMS) related to the higher clinical and angiographic complexity of off-label patients (1,7–13). Notwithstanding, the higher efficacy of DES over BMS was confirmed also in this high-risk patient subset, with a substantial reduction in repeat revascularization and without major concerns with respect to safety (1,7–15).

Most of the aforementioned studies were observational and focused on early-generation DES, whereas the outcomes of newer-generation DES have not been reported among patients with complex clinical and angiographic features. All-comers randomized clinical trials are performed with the aim to investigate the safety and efficacy of DES in a real-world population including the entire clinical spectrum of patient and lesion complexity (16–19). The recently published RESOLUTE All Comers trial (A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention) is the largest randomized DES all-comers trial to date and showed noninferior clinical and angiographic outcomes of the unrestricted use of the Resolute zotarolimus-eluting stent (ZES) (Medtronic CardioVascular, Santa Rosa, California) compared with the XIENCE V everolimus-eluting stent (EES) (Abbott Vascular Devices, Santa Clara, California) (19). We performed a stratified analysis of clinical and angiographic outcomes according to patient and lesion complexity in the RESOLUTE All Comers trial and compared the relative safety and efficacy of ZES and EES in complex and simple patients.

Methods

Study population. The RESOLUTE All Comers trial is an unrestricted, open-label, randomized, controlled, multicenter trial (19). In brief the study applied an all-comers approach to recruit 2,292 patients with chronic stable coronary artery disease or acute coronary syndromes including ST-segment elevation myocardial infarction (MI), who were eligible for enrolment if they had ≥1 lesion with diameter stenosis ≥50% and a reference vessel diameter between 2.25 and 4.0 mm. No restriction was placed on the number of lesions or vessels treated or the number of stents implanted. Principal exclusion criteria were allergy to study medication, metal alloys, or contrast media; planned surgery within 6 months of percutaneous coronary intervention (PCI) unless the dual antiplatelet therapy could be maintained throughout the peri-operative period; pregnancy; participation in another trial before reaching the primary endpoint; and inability to give informed consent.

The definition of complex patients was pre-specified and included clinical and angiographic characteristics. Patients were considered complex if they had at least 1 of the following features: acute MI within 72 h, left ventricular ejection fraction <30%, renal insufficiency or failure (creatinine ≥140 μmol/l), treatment of bifurcations, saphenous vein grafts, arterial grafts, in-stent restenosis, unprotected left main lesions, more than 2 vessels treated, lesion length >27 mm, more than 1 lesion/vessel, lesions with thrombus, or lesions with total occlusion (pre-procedure Thrombolysis In Myocardial Infarction flow grade 0). The study complied with the Declaration of Helsinki and was approved by all institutional ethics committees. All patients provided written, informed consent for participation in the trial.

Randomization and procedures. Patients were randomly assigned on a 1:1 basis to treatment with either ZES or EES and to 12-month clinical follow-up only or active angiographic follow-up at 13 months, on a 4:1 basis with a factorial design. A blinded independent clinical events committee adjudicated all endpoints, and independent study monitors verified all case reports from data on-site. The operators were, by necessity, aware of the assigned study stent during PCI and angiographic follow-up, but patients

From the *Bern University Hospital, Bern, Switzerland; †Erasmus Medical Center, Rotterdam, the Netherlands; ‡Kardiologische Praxis und Praxisklinik, Munich, Germany; §Herzzentrum, Segeberger Kliniken, Bad Segeberg, Germany; ‖Medical University of Silesia, Katowice, Poland; ¶Rigshospitalet, Copenhagen, Denmark; #Medisch Centrum Leeuwarden, Leeuwarden, the Netherlands; **Herzzentrum Leipzig, Leipzig, Germany; ††Department of Cardiology, University Hospital Munich (Innenstadt), Munich, Germany; ‡‡Cardiovascular Center Aalst, OLV Hospital, Aalst, Belgium; §§Servicio de Cardiología, Hospital Universitario, Madrid, Spain; ‖‖Institut Cardiovasculaire Paris-Sud, Quincy, France; ¶¶Department of Cardiology, Royal Brompton Hospital, London, United Kingdom; ##Royal Victoria Hospital, Belfast, United Kingdom; ***Department of Cardiology, Rabin Medical Center, Tel Aviv University, Tel Aviv, Israel; †††Department of Cardiology, Hospital Bogenhausen, Munich, Germany; ‡‡‡Centro Cardiologico Monzino, IRCCS, University of Milan, Milan, Italy; and §§§Cardialysis, Rotterdam, the Netherlands. The RESOLUTE All Comers trial was supported by Medtronic CardioVascular. Dr. Silber has served on the Advisory Board for Medtronic. Dr. Linke has served as consultant for Medtronic. Dr. Di Mario has received Speakers' Bureau fees from Medtronic. Dr. Manoharan has served as consultant for Medtronic. Dr. Windecker has received lecture and consulting fees from Abbott, Cordis, Biosensors, Boston Scientific, and Medtronic. All other authors have reported that they have no relationships to disclose.

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and staff involved in follow-up assessment were blinded to the allocated stent type.

The ZES were available in diameters of 2.25 to 4.0 mm and in lengths of 8 to 30 mm, whereas EES were available in diameters of 2.25 to 4.0 mm and in lengths of 8 to 28 mm. Balloon angioplasty and stent implantation were performed according to standard technique, and direct stenting was allowed. The aim was to obtain full lesion coverage with 1 or several stents. No mixture of DES was permitted within a given patient, unless the operator was unable to insert the study stent, in which case crossover to another device of the operator's choice was possible.

Procedural anticoagulation was achieved with unfractionated heparin 5,000 IU or 70 to 100 IU/kg or bivalirudin 0.75 mg/kg bolus followed by 1.75 mg/kg/h infusion. The use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator. Before the procedure, all patients enrolled into the study received at least 75 mg of acetylsalicylic acid, whereas the 300- to 600-mg loading dose of clopidogrel was only given if no clopidogrel had been administrated daily in the previous 7 days. All patients were discharged on at least 75 mg of acetylsalicylic acid indefinitely and clopidogrel 75 mg for >6 months after the index procedure. In case of intercurrent revascularization procedures requiring stent implantation, treating cardiologists were encouraged to use study stents.

Adverse events were assessed in hospital, and clinical follow-up was performed at 1, 6, and 12 months. Angiographic follow-up at 13 months was planned in a randomized subset of patients (20%).

Quantitative coronary angiography. Quantitative coronary angiography was performed with the CAAS II analysis system (Pie Medical BV, Maastricht, the Netherlands). Quantitative coronary angiography and SYNTAX score calculation were centrally assessed at an angiographic core laboratory (Cardialysis, Rotterdam, the Netherlands) (20). Additional quantitative coronary angiography methodology and definitions are fully described elsewhere (19).

Study endpoints. The primary endpoint of this analysis was target lesion failure (TLF) at 12-month follow-up, defined as a composite of cardiac death, target vessel MI, and clinically indicated target lesion revascularization (TLR). Secondary clinical endpoints were: a patient-oriented composite endpoint including all cause death, any MI, and any repeat revascularization; target vessel failure, defined as a composite of cardiac death, target-vessel MI, and clinically indicated target vessel revascularization; the individual components of the composite primary and secondary endpoints; and Academic Research Consortium–

Table 1 Baseline Clinical Characteristics Stratified by Complexity

	Complex Patients			Simple Patients		
	ZES (n = 764)	EES (n = 756)	p Value	ZES (n = 376)	EES (n = 396)	p Value
Age, yrs	64.0 ± 11.1	63.7 ± 11.0	0.68	65.1 ± 10.3	65.0 ± 10.3	0.88
Male	78.3%	79.6%	0.53	73.4%	72.5%	0.81
BMI, kg/m^2	27.9 ± 4.5	27.8 ± 4.3	0.72	27.7 ± 4.2	27.7 ± 4.4	0.90
Cardiac risk factors						
Hypertension	70.3%	69.6%	0.78	72.6%	74.5%	0.57
Hyperlipidemia	61.5%	64.7%	0.20	68.9%	73.5%	0.18
Diabetes mellitus	24.0%	22.2%	0.43	22.6%	25.8%	0.31
Insulin dependent	8.6%	6.7%	0.18	8.0%	7.8%	1.00
Current smoking	28.7%	30.3%	0.50	22.1%	19.2%	0.33
Premature CAD in first-degree relative	34.1%	36.8%	0.32	34.0%	36.5%	0.51
Previous MI	29.0%	30.2%	0.61	28.7%	31.0%	0.52
Previous PCI	33.5%	31.3%	0.38	28.5%	33.6%	0.14
Previous CABG	11.1%	10.6%	0.74	7.7%	7.6%	1.00
Clinical characteristics						
Stable angina	27.1%	26.9%	0.95	46.5%	53.8%	0.05
Unstable angina	14.1%	15.1%	0.61	30.1%	26.3%	0.26
Acute MI within 72 h	43.2%	43.9%	0.80	0.0%	0.0%	—
ST-segment elevation MI	20.5%	24.6%	0.07	0.0%	0.0%	—
Non–ST-segment elevation MI	22.6%	19.3%	0.12	0.0%	0.0%	—
Left ventricular ejection fraction			0.74			0.43
<30%	4.1%	3.4%		0.0%	0.0%	
30%–50%	32.3%	32.1%		26.8%	23.4%	
>50%	63.6%	64.5%		73.2%	76.6%	
Multivessel disease	61.6%	60.8%	0.75	51.9%	56.1%	0.25

Values are mean ± SD or %.

BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; EES = everolimus-eluting stent(s); MI = myocardial infarction; PCI = percutaneous coronary intervention; ZES = zotarolimus-eluting stent(s).

defined definite, probable, and overall ST at various time points. The secondary angiographic endpoint was in-stent percentage diameter stenosis. Additional angiographic measures included in-segment percentage diameter stenosis, in-stent and in-segment minimal lumen diameter, late loss, and binary restenosis.

All deaths were considered cardiac unless an undisputed noncardiac cause was present. MI was defined according to an extended historical definition (21). MI was considered related to the target vessel unless clearly attributable to a non-target vessel. A Q-wave MI required, in the absence of cardiac enzyme data, a history of chest pain or other acute symptoms consistent with myocardial ischemia together with new pathological Q waves in 2 or more contiguous electrocardiographic (ECG) leads as assessed by the core laboratory or clinical events committee. In the presence of elevated cardiac enzymes, new pathological Q waves in 2 or more contiguous ECG leads as assessed by the core laboratory or clinical events committee were sufficient to diagnose a Q-wave MI. In the absence of an ECG, a Q-wave MI could be adjudicated on the basis of the clinical scenario and appropriate cardiac enzyme data. A revascularization was considered clinically indicated if angiography during follow-up showed a diameter stenosis ≥50% (core laboratory quantitative assessment) and if 1 of the following occurred: 1) a positive history of recurrent angina pectoris, presumably related to the target vessel; 2) objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel; 3) abnormal results of any invasive functional diagnostic test (e.g., fractional flow reserve); or 4) a TLR with a diameter stenosis ≥70% even in the absence of the aforementioned ischemic signs or symptoms. Stent thrombosis was defined according to the Academic Research Consortium criteria (22).

Statistical methods. The RESOLUTE All Comers trial was powered for noninferiority testing of the primary

Table 2 Baseline Lesion Characteristics Stratified by Complexity

	Complex Patients			Simple Patients		
	ZES (n = 1,227 Lesions)	EES (n = 1,242 Lesions)	p Value	ZES (n = 434 Lesions)	EES (n = 463 Lesions)	p Value
Vessel location (per patient)						
Left main	3.0%	3.2%	0.88	0.5%	1.3%	0.45
Left anterior descending	53.1%	48.9%	0.11	51.6%	48.0%	0.35
Left circumflex	34.0%	33.6%	0.87	30.9%	31.6%	0.88
Right	39.7%	44.0%	0.09	32.4%	36.1%	0.29
Bypass graft	3.7%	3.7%	1.00	0.0%	0.0%	—
Saphenous vein graft	3.3%	3.7%	0.68	0.0%	0.0%	—
Arterial graft	0.5%	0.0%	0.12	0.0%	0.0%	—
ACC/AHA lesion class			0.71			0.32
A	2.0%	2.2%		2.3%	2.0%	
B1	17.7%	19.0%		28.0%	33.7%	
B2	27.0%	25.3%		35.0%	33.0%	
C	53.3%	53.4%		34.7%	31.3%	
Lesions with thrombus	7.3%	6.8%	0.68	0.0%	0.0%	—
Ostial lesions	4.1%	3.8%	0.67	4.2%	2.2%	0.12
Lesion with calcifications			0.20			0.37
Little or none	79.1%	81.3%		75.0%	77.6%	
Moderate-to-heavy	20.9%	18.7%		25.0%	22.4%	
TIMI flow grade			0.73			0.86
0	16.6%	17.6%		0.0%	0.0%	
1	3.1%	2.7%		2.8%	3.7%	
2	6.0%	5.7%		7.7%	6.3%	
3	74.4%	73.9%		89.5%	90.0%	
Angiographic measures						
Lesion length, mm	12.11 ± 8.30	12.61 ± 8.83	0.21	11.38 ± 5.16	11.18 ± 5.12	0.56
Reference vessel diameter, mm	2.61 ± 0.59	2.62 ± 0.58	0.66	2.67 ± 0.54	2.63 ± 0.56	0.29
Minimal lumen diameter, mm	0.90 ± 0.57	0.88 ± 0.55	0.44	1.11 ± 0.39	1.07 ± 0.41	0.17
Stenosis (% of lumen diameter)	65.5 ± 19.8	66.1 ± 19.6	0.42	58.2 ± 12.2	59.1 ± 12.7	0.31
Patient-based lesion characteristics						
SYNTAX score	16.6 ± 9.4	16.5 ± 9.4	0.94	11.2 ± 7.9	10.9 ± 7.5	0.64
Patients with at least 1 bifurcation	25.1%	27.0%	0.41	0.0%	0.0%	—
Patients with at least 1 in-stent restenosis	12.0%	12.1%	1.00	0.0%	0.0%	—
Patients with at least 1 total occlusion	24.3%	26.2%	0.41	0.0%	0.0%	—

Values are % or mean ± SD.
ACC/AHA = American College of Cardiology/American Heart Association; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

endpoint at 12 months on an intention-to-treat basis. For full details of the sample size calculation with respect to the noninferiority primary and secondary endpoints, we refer to the main paper (19). The complex patient cohort was defined according to the pre-specified definition. The simple patient cohort comprised all patients who were not complex. For both complex and simple patients, patients treated with ZES were compared with patients treated with EES, and p values were calculated by Fisher exact test for binary variables, Cochran-Mantel-Haenszel test for multicategorical variables, and *t* test for continuous variables. The interaction p values were calculated for the clinical and angiographic outcomes, with logistic regression or linear regression, respectively. The time to the clinical endpoints was calculated with the method of Kaplan-Meier. A 2-sided p value <0.05 was considered statistically significant, unless otherwise specified.

Results

Among 2,292 patients included in the RESOLUTE All Comers trial, 1,520 were complex according to the pre-specified definition, whereas 772 had simple characteristics. Of 1,520 complex patients, 764 patients with 1,227 lesions were allocated to treatment with ZES, and 756 patients with 1,242 lesions were allocated to treatment with EES. Of 772 simple patients, 376 patients with 434 lesions were allocated to treatment with ZES, and 396 patients with 463 lesions were allocated to treatment with EES. Baseline clinical variables were well-balanced between ZES and EES among both complex and simple patients (Table 1). Complex as compared with simple patients were younger (age 63.9 ± 11.1 years vs. 65.1 ± 10.3 years, p = 0.008), more frequently male (78.9% vs. 72.9%, p = 0.001) and smoking (29.5% vs. 20.6%, p < 0.001), and had hyperlipidemia less frequently (63.1% vs. 71.2%, p < 0.001) and previous coronary artery bypass surgery more frequently (10.9% vs. 7.6%, p = 0.014). Target lesion and angiographic characteristics at baseline revealed no differences between ZES and EES among complex and simple patients (Table 2). Procedural and angiographic results are summarized in Table 3, showing similar outcomes for ZES and EES in complex and simple patients. Differences in clinical indication and angiographic characteristics including the SYNTAX score between complex and simple patients were driven by the pre-specified definition of complexity. Clinical outcomes were obtained for 2,245 (97.9%) of the 2,292 randomized patients during 1 year of follow-up. Twenty-one patients lost to follow-up belonged to the ZES group, and 26 patients belonged to the EES group.

Clinical outcomes. Rates of TLF (9.3% vs. 6.3%, p = 0.015), target vessel failure (10.4% vs. 7.1%, p = 0.009), and the patient-oriented composite endpoint (16.1% vs. 11.6%, p = 0.004) were higher among complex than simple patients at 1 year.

Clinical events stratified for complexity are summarized in Table 4. Among complex patients, the primary endpoint TLF—a composite of cardiac death, target-vessel MI, and clinically indicated TLR—was similar for both stent types, occurring in 67 (8.9%) ZES patients and 72 (9.7%) EES patients (risk difference of −0.8% [95% confidence interval (CI): −3.7% to 2.2%]) (Fig. 1). Similarly, the patient-oriented endpoint—a composite of all-cause death, any MI, and any repeat revascularization—showed no difference between ZES- (15.6%) and EES-treated (16.6%) complex patients (risk difference of −1.0% [95% CI: −4.7% to 2.7%]) (Fig. 2). Rates of all-cause death were lower among ZES- than EES-treated complex patients at 1 year (1.5% vs. 3.4%, p = 0.02), mainly driven by a significant difference

Table 3 Procedural Results Stratified by Complexity

	Complex Patients			Simple Patients		
	ZES	EES	p Value	ZES	EES	p Value
Treated lesions/patient (index and staged), n	1.61 ± 0.81	1.64 ± 0.87	0.39	1.15 ± 0.38	1.17 ± 0.38	0.59
Patients with staged procedure, n	11.4%	12.0%	0.75	1.6%	3.8%	0.08
Stents/lesion, n	1.15 ± 0.41	1.20 ± 0.47	0.004	1.16 ± 0.45	1.15 ± 0.39	0.88
Minimal stent diameter, mm	2.96 ± 0.47	2.97 ± 0.48	0.69	2.98 ± 0.45	3.04 ± 0.46	0.05
Stent length/lesion, mm	21.15 ± 9.66	22.13 ± 10.38	0.01	20.03 ± 10.01	20.43 ± 9.42	0.51
Maximal pressure/lesion, atm	14.92 ± 3.16	15.09 ± 3.16	0.15	14.80 ± 2.83	14.77 ± 3.24	0.88
Angiographic results						
Final minimal lumen diameter, mm						
In-stent	2.34 ± 0.53	2.35 ± 0.54	0.51	2.45 ± 0.47	2.46 ± 0.50	0.82
In-segment	2.03 ± 0.54	2.04 ± 0.56	0.66	2.13 ± 0.52	2.11 ± 0.52	0.55
Final stenosis, % of lumen diameter						
In-stent	15.2 ± 11.4	14.8 ± 11.1	0.40	12.9 ± 7.8	12.5 ± 8.6	0.50
In-segment	23.6 ± 12.2	23.3 ± 12.0	0.46	22.4 ± 10.3	22.3 ± 10.5	0.90
Acute gain, mm						
In-stent	1.44 ± 0.61	1.48 ± 0.64	0.15	1.35 ± 0.46	1.39 ± 0.47	0.28
In-segment	1.13 ± 0.62	1.17 ± 0.65	0.17	1.04 ± 0.49	1.05 ± 0.50	0.78

Values are mean ± SD or %.
Abbreviations as in Table 1.

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Table 4 Clinical Events at 30 and 360 Days Stratified by Complexity

	Complex Patients				Simple Patients				
	ZES (n = 764)	EES (n = 756)	Difference [95% CI]	p Value	ZES (n = 376)	EES (n = 396)	Difference [95% CI]	p Value	p Value for Interaction*
Events at 30 days									
Death	0.3%	1.2%	−0.9% [−1.8% to −0.1%]	0.04	0.0%	0.3%	−0.3% [−0.8% to 0.2%]	1.00	0.97
Cardiac death	0.3%	0.9%	−0.7% [−1.4% to 0.1%]	0.11	0.0%	0.3%	−0.3% [−0.8% to 0.2%]	1.00	0.97
Target vessel MI	3.6%	4.0%	−0.4% [−2.4% to 1.5%]	0.69	2.9%	3.0%	−0.1% [−2.5% to 2.3%]	1.00	0.86
Q-wave	0.5%	0.5%	−0.0% [−0.7% to 0.7%]	1.00	0.3%	0.3%	0.0% [−0.7% to 0.7%]	1.00	0.97
Non–Q-wave	3.2%	3.5%	−0.3% [−2.1% to 1.5%]	0.77	2.7%	2.8%	−0.1% [−2.4% to 2.2%]	1.00	0.92
Non–target vessel MI	0.1%	0.1%	−0.0% [−0.4% to 0.4%]	1.00	0.3%	0.0%	0.3% [−0.3% to 0.8%]	0.49	0.97
Q-wave	0.1%	0.1%	−0.0% [−0.4% to 0.4%]	1.00	0.0%	0.0%	0.0% [— to —]	—	1.00
Non–Q-wave	0.0%	0.0%	0.0% [— to —]	—	0.3%	0.0%	0.3% [−0.3% to 0.8%]	0.49	0.98
Clinically indicated TLR	1.3%	0.7%	0.7% [−0.3% to 1.6%]	0.30	1.3%	0.8%	0.6% [−0.9% to 2.0%]	0.49	0.90
Percutaneous	1.3%	0.4%	0.9% [−0.0% to 1.8%]	0.09	0.8%	0.5%	0.3% [−0.8% to 1.4%]	0.68	0.51
Surgical	0.0%	0.3%	−0.3% [−0.6% to 0.1%]	0.25	0.5%	0.3%	0.3% [−0.6% to 1.2%]	0.61	0.97
Clinically indicated TVR	1.7%	0.9%	0.8% [−0.4% to 1.9%]	0.26	1.3%	0.8%	0.6% [−0.9% to 2.0%]	0.49	0.96
Percutaneous	1.7%	0.7%	1.0% [−0.0% to 2.1%]	0.09	0.8%	0.5%	0.3% [−0.8% to 1.4%]	0.68	0.64
Surgical	0.0%	0.3%	−0.3% [−0.6% to 0.1%]	0.25	0.5%	0.3%	0.3% [−0.6% to 1.2%]	0.61	0.97
Any revascularization	2.8%	2.1%	0.6% [−0.9% to 2.2%]	0.51	2.1%	1.3%	0.9% [−1.0% to 2.7%]	0.41	0.69
Cardiac death or TV MI	3.8%	4.7%	−0.8% [−2.9% to 1.2%]	0.44	2.9%	3.3%	−0.4% [−2.8% to 2.1%]	0.84	0.85
Death or TV MI	3.8%	4.9%	−1.1% [−3.2% to 1.0%]	0.31	2.9%	3.3%	−0.4% [−2.8% to 2.1%]	0.84	0.76
TLF	4.5%	5.2%	−0.7% [−2.9% to 1.4%]	0.55	3.8%	3.8%	−0.1% [−2.8% to 2.6%]	1.00	0.75
TVF	4.7%	5.5%	−0.7% [−2.9% to 1.5%]	0.56	3.8%	3.8%	−0.1% [−2.8% to 2.6%]	1.00	0.76
Composite endpoint	5.9%	6.8%	−0.9% [−3.3% to 1.6%]	0.53	4.6%	4.3%	0.2% [−2.7% to 3.2%]	1.00	0.62
Events at 360 days									
Death	1.5%	3.4%	−1.9% [−3.5% to −0.4%]	0.02	1.9%	1.6%	0.3% [−1.5% to 2.2%]	0.78	0.11
Cardiac death	1.3%	2.2%	−0.8% [−2.2% to 0.5%]	0.24	1.4%	0.8%	0.6% [−0.9% to 2.1%]	0.50	0.21
Target vessel MI	4.3%	4.4%	−0.2% [−2.3% to 1.9%]	0.90	4.1%	3.4%	0.7% [−2.0% to 3.4%]	0.70	0.60
Q-wave	0.7%	0.5%	0.1% [−0.7% to 0.9%]	1.00	0.8%	0.3%	0.6% [−0.5% to 1.6%]	0.36	0.48
Non–Q-wave	3.7%	3.9%	−0.2% [−2.1% to 1.8%]	0.89	3.3%	3.1%	0.1% [−2.4% to 2.7%]	1.00	0.84
Non–target vessel MI	0.3%	0.4%	−0.1% [−0.7% to 0.4%]	0.68	0.8%	0.0%	0.8% [−0.1% to 1.7%]	0.12	0.97
Q-wave	0.1%	0.1%	−0.0% [−0.4% to 0.4%]	1.00	0.3%	0.0%	0.3% [−0.3% to 0.8%]	0.49	0.97
Non–Q-wave	0.1%	0.3%	−0.1% [−0.6% to 0.3%]	0.62	0.5%	0.0%	0.5% [−0.2% to 1.3%]	0.24	0.97
Clinically indicated TLR	4.4%	4.0%	0.3% [−1.7% to 2.4%]	0.80	3.0%	2.1%	0.9% [−1.3% to 3.2%]	0.49	0.59
Percutaneous	4.0%	3.2%	0.8% [−1.1% to 2.6%]	0.49	2.2%	1.8%	0.4% [−1.6% to 2.4%]	0.80	0.95
Surgical	0.4%	0.9%	−0.5% [−1.4% to 0.3%]	0.22	0.8%	0.3%	0.6% [−0.5% to 1.6%]	0.36	0.13
Clinically indicated TVR	5.6%	5.5%	0.1% [−2.3% to 2.4%]	1.00	3.5%	3.4%	0.2% [−2.5% to 2.8%]	1.00	0.94
Percutaneous	5.1%	4.9%	0.2% [−2.0% to 2.4%]	0.90	2.7%	3.1%	−0.4% [−2.8% to 2.0%]	0.83	0.71
Surgical	0.5%	1.1%	−0.5% [−1.5% to 0.4%]	0.26	0.8%	0.3%	0.6% [−0.5% to 1.6%]	0.36	0.15
Any revascularization	11.3%	10.1%	1.2% [−1.9% to 4.3%]	0.50	8.7%	7.0%	1.7% [−2.2% to 5.5%]	0.42	0.73
Cardiac death or TV MI	5.5%	6.2%	−0.7% [−3.1% to 1.6%]	0.58	5.2%	3.9%	1.3% [−1.7% to 4.3%]	0.48	0.30
Death or TV MI	5.6%	7.4%	−1.8% [−4.3% to 0.7%]	0.17	5.7%	4.4%	1.3% [−1.8% to 4.4%]	0.51	0.15
TLF	8.9%	9.7%	−0.8% [−3.7% to 2.2%]	0.66	6.8%	5.7%	1.1% [−2.4% to 4.6%]	0.55	0.43
TVF	9.8%	11.1%	−1.2% [−4.3% to 1.9%]	0.45	7.4%	6.8%	0.6% [−3.1% to 4.3%]	0.78	0.51
Composite endpoint	15.6%	16.6%	−1.0% [−4.7% to 2.7%]	0.62	12.5%	10.7%	1.9% [−2.7% to 6.4%]	0.49	0.34

Values are %. *p values for interaction relate to differences in risk difference between complex and simple patients.

CI = confidence interval; Composite endpoint = composite of death, myocardial infarction, any revascularization); TLF = target lesion failure (composite of cardiac death, target vessel myocardial infarction, clinically indicated target lesion revascularization); TLR = target lesion revascularization; TV = target vessel; TVF = target vessel failure (composite of cardiac death, target vessel myocardial infarction, clinically indicated target vessel revascularization); TVR = target vessel revascularization; other abbreviations as in Table 1.

in noncardiac deaths (ZES: 0.1% vs. EES: 1.2%, p = 0.01). Event rates were similar for ZES- and EES-treated complex patients with respect to cardiac death (1.3% vs. 2.2%, p = 0.24), target-vessel MI (4.3% vs. 4.4%, p = 0.90), and clinically indicated TLR (4.4% vs. 4.0%, p = 0.80). Among simple patients, rates of TLF (6.8% vs. 5.7%, risk difference of 1.1% [95% CI: −2.4% to 4.6%, p = 0.55]) and the patient-oriented composite endpoint (12.5% vs. 10.7%, risk difference of 1.9% [95% CI: −2.7% to 6.4%, p = 0.49]) were comparable for ZES and EES, as were the individual components of the primary endpoint (Table 4). Definite or probable ST occurred in 20 (1.3%) complex patients with no significant difference between ZES and EES (1.7% vs. 0.9%, p = 0.26). Among simple patients, definite or probable ST was observed in 5 (1.4%) patients treated with ZES and 1 (0.3%) patient treated with EES (p = 0.12).

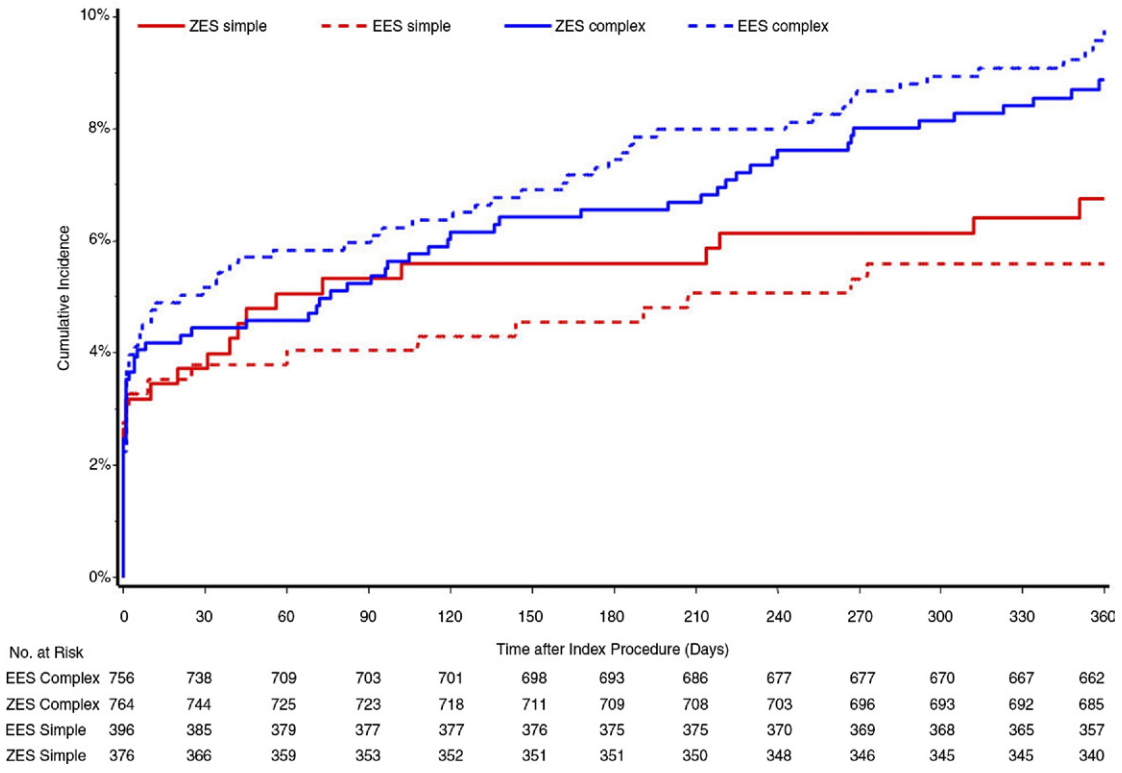

Figure 1 **Target Lesion Failure Stratified for Complexity and Stent Type**

Kaplan-Meier cumulative incidence of target lesion failure—composite of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revascularization stratified according to complexity and stent type. EES = everolimus-eluting stent(s); ZES = zotarolimus-eluting stent(s).

Rates of definite, definite or probable, and overall ST at various time points are summarized in Table 5. The mean duration of dual antiplatelet therapy was similar among complex (ZES: 329.6 ± 74.1 days; EES: 324.9 ± 79.4 days, p = 0.24) and simple patients (ZES: 325.7 ± 80.3 days; EES: 330.6 ± 69.9 days, p = 0.37). Of note: of 16 patients suffering definite ST, there was only 1 case of a complex patient treated with ZES who had discontinued clopidogrel 3 days before ST.

Angiographic outcomes. Angiographic follow-up at 13 months was obtained in 137 complex ZES and 138 complex EES lesions as well as in 54 simple ZES and 48 simple EES lesions. Quantitative coronary angiographic findings during follow-up are shown in Table 6. Among lesions in complex patients, the secondary angiographic endpoint in-stent percentage diameter stenosis (ZES: 22.2 ± 15.4% vs. EES: 21.4 ± 15.8%, p = 0.67) as well as in-stent late loss (ZES: 0.26 ± 0.48 mm vs. EES: 0.23 ± 0.44 mm, p = 0.75) and in-segment binary restenosis (6.6% vs. 8.0%, p = 0.82) were similar for ZES and EES. Conversely, in-stent percentage diameter stenosis (20.2 ± 11.6 vs. 15.0 ± 9.0, p = 0.01) and in-stent late loss (0.29 ± 0.27 vs. 0.07 ± 0.25, p < 0.001) were lower with EES than ZES among lesions in simple patients, although formal tests for interaction failed to reach conventional levels of significance (Fig. 3). In-segment binary restenosis in lesions of simple patients was low and comparable for both stent types (1.9% vs. 2.1%, p = 1.00).

Discussion

This is the first report investigating the impact of patient and lesion complexity on clinical and angiographic outcomes with the unrestricted use of 2 newer-generation DES in a large-scale, randomized clinical trial. The findings can be summarized as follows:

1. Newer-generation DES are safe and effective among patients with complex baseline clinical and angiographic characteristics through 1 year.
2. The ZES and EES achieve similar clinical outcomes, regardless of patient complexity through 1 year.
3. The ZES and EES yield similar angiographic results particularly among complex patients.
4. Newer-generation DES are associated with low rates of ST in both complex and simple patient populations.

Several studies investigating the safety and effectiveness of early-generation DES in complex patients with off-label characteristics showed a less-favorable outcome compared with patients with simple on-label features (7–15). A large meta-analysis confirmed the higher efficacy of DES over BMS

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Figure 2 Patient-Oriented Composite Endpoint Stratified for Complexity and Stent Type

Kaplan-Meier cumulative incidence of the patient-oriented composite endpoint—composite of all-cause death, myocardial infarction, and repeat revascularization stratified according to complexity and stent type. Abbreviations as in Figure 1.

Table 5 ARC-Defined ST Stratified by Complexity

	Complex Patients				Simple Patients				
	ZES (n = 764)	EES (n = 756)	Difference [95% CI]	p Value	ZES (n = 376)	EES (n = 396)	Difference [95% CI]	p Value	p Value for Interaction*
Definite ST									
Acute	0.4%	0.1%	0.3% [−0.3% to 0.8%]	0.62	0.3%	0.0%	0.3% [−0.3% to 0.8%]	0.49	0.98
Subacute	0.5%	0.0%	0.5% [0.0% to 1.1%]	0.12	0.3%	0.0%	0.3% [−0.3% to 0.8%]	0.49	1.00
Early	0.9%	0.1%	0.8% [0.1% to 1.5%]	0.07	0.5%	0.0%	0.5% [−0.2% to 1.3%]	0.24	0.97
Late	0.4%	0.3%	0.1% [−0.5% to 0.7%]	1.00	0.5%	0.0%	0.5% [−0.2% to 1.3%]	0.24	0.97
Overall	1.2%	0.4%	0.8% [−0.1% to 1.7%]	0.14	1.1%	0.0%	1.1% [0.0% to 2.2%]	0.06	0.98
Definite or probable ST									
Acute	0.5%	0.3%	0.3% [−0.4% to 0.9%]	0.69	0.3%	0.0%	0.3% [−0.3% to 0.8%]	0.49	0.98
Subacute	0.9%	0.4%	0.5% [−0.3% to 1.4%]	0.34	0.3%	0.3%	0.0% [−0.7% to 0.7%]	1.00	0.61
Early	1.3%	0.7%	0.7% [−0.4% to 1.7%]	0.30	0.5%	0.3%	0.3% [−0.6% to 1.2%]	0.62	0.97
Late	0.5%	0.3%	0.3% [−0.4% to 0.9%]	0.69	0.8%	0.0%	0.8% [−0.1% to 1.7%]	0.12	0.97
Overall	1.7%	0.9%	0.8% [−0.4% to 1.9%]	0.26	1.4%	0.3%	1.1% [−0.2% to 2.4%]	0.12	0.38
Definite, probable, or possible ST									
Acute	0.5%	0.3%	0.3% [−0.4% to 0.9%]	0.69	0.3%	0.0%	0.3% [−0.3% to 0.8%]	0.49	0.98
Subacute	0.9%	0.4%	0.5% [−0.3% to 1.4%]	0.34	0.3%	0.3%	0.0% [−0.7% to 0.7%]	1.00	0.61
Early	1.3%	0.7%	0.7% [−0.4% to 1.7%]	0.30	0.5%	0.3%	0.3% [−0.6% to 1.2%]	0.62	0.98
Late	1.2%	1.3%	−0.2% [−1.3% to 1.0%]	0.82	1.6%	0.3%	1.4% [−0.0% to 2.8%]	0.06	0.09
Overall	2.4%	2.0%	0.4% [−1.1% to 1.9%]	0.73	2.2%	0.5%	1.7% [0.0% to 3.3%]	0.06	0.14

Values are %. *p values for interaction relate to differences in risk difference between complex and simple patients.
ARC = Academic Research Consortium; ST = stent thrombosis; other abbreviations as in Tables 1 and 4.

Table 6 Angiographic Results at 13 Months Stratified by Complexity

	Complex Patients				Simple Patients				
	ZES (n = 137 Lesions)	EES (n = 138 Lesions)	Difference [95% CI]	p Value	ZES (n = 54 Lesions)	EES (n = 48 Lesions)	Difference [95% CI]	p Value	p Value for Interaction*
Reference vessel diameter, mm	2.80 ± 0.62	2.68 ± 0.52	0.1 [−0.0 to 0.3]	0.09	2.67 ± 0.55	2.69 ± 0.50	−0.0 [−0.2 to 0.2]	0.84	0.29
Minimal lumen diameter, mm									
In-stent	2.21 ± 0.66	2.16 ± 0.59	0.05 [−0.10 to 0.20]	0.49	2.15 ± 0.51	2.40 ± 0.53	−0.24 [−0.45 to −0.04]	0.02	0.04
In-segment	2.05 ± 0.63	1.97 ± 0.58	0.07 [−0.07 to 0.21]	0.33	1.98 ± 0.54	2.06 ± 0.52	−0.07 [−0.28 to 0.13]	0.48	0.28
Stenosis, % of lumen diameter									
In-stent	22.2 ± 15.4	21.4 ± 15.8	0.81 [−2.90 to 4.52]	0.67	20.2 ± 11.6	15.0 ± 9.0	5.18 [1.05 to 9.31]	0.01	0.19
In-segment	26.8 ± 15.0	26.2 ± 16.1	0.60 [−3.09 to 4.29]	0.75	25.9 ± 11.3	23.6 ± 11.3	2.26 [−2.20 to 6.72]	0.32	0.62
Late loss, mm									
In-stent	0.26 ± 0.48	0.23 ± 0.44	0.03 [−0.08 to 0.14]	0.58	0.29 ± 0.27	0.07 ± 0.25	0.21 [0.11 to 0.32]	<0.001	0.07
In-segment	0.14 ± 0.47	0.08 ± 0.45	0.07 [−0.05 to 0.18]	0.25	0.16 ± 0.29	−0.01 ± 0.20	0.17 [0.06 to 0.27]	0.001	0.31
Binary restenosis									
In-stent	5.1%	5.1%	0.0% [−5.2% to 5.2%]	1.00	1.9%	0.0%	1.9% [−1.7% to 5.4%]	1.00	0.97
In-segment	6.6%	8.0%	−1.4% [−7.5% to 4.7%]	0.82	1.9%	2.1%	−0.2% [−5.6% to 5.2%]	1.00	0.95

Values are mean ± SD or %. *p values for interaction relate to differences in risk difference between complex and simple patients.
Abbreviations as in Tables 1 and 4.

among off-label patients, with a substantial reduction in the risk of target vessel revascularization (hazard ratio: 0.45, $p < 0.001$) and no concern with respect to safety (1), although most of these data were observational and limited to early-generation DES. More recently, the newer-generation EES has been shown to improve upon the safety and efficacy profile, compared with the early-generation paclitaxel-eluting stent, and the newer-generation ZES has been shown to be noninferior to EES (18,23). However, no study has focused on the differential outcome of newer-generation DES among patients with complex clinical and angiographic characteristics typically excluded from pre-approval DES trials.

Against this background, we compared clinical and angiographic outcomes between ZES and EES among complex as well as simple patients included in the RESOLUTE All Comers trial. In this largest all-comers study, the unrestricted use of ZES and EES was tested in patients covering a wide range of clinical and angiographic complexities. The pre-specified definition of complex patients encompassed real-world characteristics, including acute MI within 72 h, left ventricular ejection fraction <30%, renal insufficiency or failure, treatment of bifurcations, saphenous vein grafts, arterial grafts, in-stent restenosis, unprotected left main lesions, more than 2 vessels treated, lesion length >27 mm, more than 1 lesion/vessel, lesion with thrombus, or lesion with total occlusion.

This definition is well in line with previous reports, as is the proportion of complex patients compared with previously reported all-comers populations (Fig. 4A). Two-thirds of patients included in the RESOLUTE All Comers trial were complex, indicating that indeed the majority of patients undergoing PCI in routine clinical practice include those typically excluded from pre-approval DES trials. Unsurprisingly, event rates were higher among complex compared with simple patients, owing to the higher prevalence of unfavorable prognostic indicators such as acute coronary syndromes, lower left ventricular ejection fraction, impaired renal function, and complex angiographic characteristics as evidenced by the higher SYNTAX score (24,25). The risk of TLF and the patient-oriented composite endpoint was increased by approximately one-third—comparing complex with simple patients. Event rates associated with the use of ZES and EES among complex and simple patients were largely comparable across all endpoints, with the exception of all-cause mortality among complex patients. However, the higher 1-year mortality associated with EES-treated complex patients was mainly due to a significantly higher rate of noncardiac deaths, whereas differences in terms of cardiac death were less pronounced.

The similar outcome between ZES and EES in terms of clinically indicated TLR and target vessel revascularization among complex patients is supported by the angiographic findings with similar in-stent minimal lumen diameter, percentage diameter stenosis, late loss, and in-segment binary restenosis at 13 months. Conversely, angiographic parameters including in-stent minimal lumen diameter,

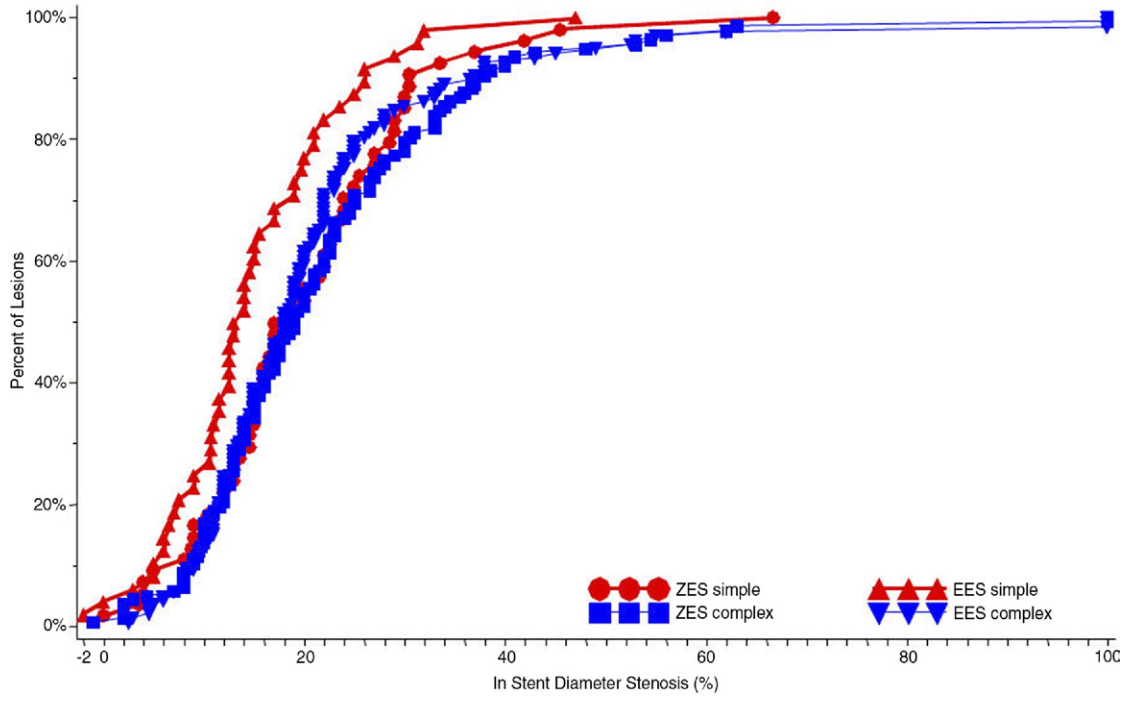

Figure 3 **Stent Percentage Diameter Stenosis Stratified for Complexity and Stent Type**

Cumulative frequency of in-stent percentage diameter stenosis stratified for stent complexity and stent type at 13-month angiographic follow-up. Abbreviations as in Figure 1.

percentage diameter stenosis, and late loss were in favor of EES among simple patients. Although formal tests for interaction reached conventional levels of significance for minimal lumen diameter, we consider these findings most likely due to chance and the low number of simple patients undergoing angiographic follow-up, because any differential outcome between the 2 devices would have been anticipated among complex patients. The favorable angiographic outcome even among complex patients with both newer-generation DES is of importance. Thus, previous studies comparing early-generation DES with surgical revascularization have shown similar outcomes in terms of safety but an increased risk of repeat revascularization among patients with 3-vessel as well as left main disease (24,25). Several randomized trials comparing EES with paclitaxel-eluting stent and an observational propensity score-matched comparison of EES with sirolimus-eluting stents have shown a lower risk of repeat revascularization with the newer-generation DES. Accordingly, the 2 newer-generation DES included in the present study might further improve on the efficacy profile of early-generation DES without compromising safety, which is of particular importance among complex patients and for future comparative trials against coronary artery bypass surgery (Fig. 4B).

Low rates of definite as well as definite or probable ST events were observed in the overall population (19), and EES was associated with a lower rate of ST, as compared with ZES. The present analysis points out that rates of ST were also low among complex patients, with overall 12 definite (0.8%) and 20 (1.3%) definite or probable events. Although there was no statistically significant difference between stent types, event rates for ST were numerically lower with EES than ZES. However, estimates of risk differences were imprecise—with wide CIs—suggesting inadequate power to detect potential differences between stent types in this subgroup analysis. Moreover, event rates for cardiac death or target vessel MI were similar for EES and ZES, suggesting that any potential difference in terms of ST failed to translate into differences in ischemic outcomes. Among simple patients, due to the very few events observed—4 definite and 6 definite or probable ST—it is difficult to interpret these findings. Overall, comparing event rates of definite ST in the present study with previously reported all-comers patient populations at 1 year, we observed event rates below 1%, which seem acceptable given the complexity of included patients and certainly testify to the progress in reducing this adverse event among patients undergoing PCI in contemporary practice (Fig. 4C).

Study limitations. The results of the present study have to be interpreted in light of the following limitations. The present report is a subgroup analysis of a randomized trial not exclusively dedicated to complex patients and was not adequately powered to detect treatment–subgroup interactions. However, patient and lesion characteristics were similar between ZES-

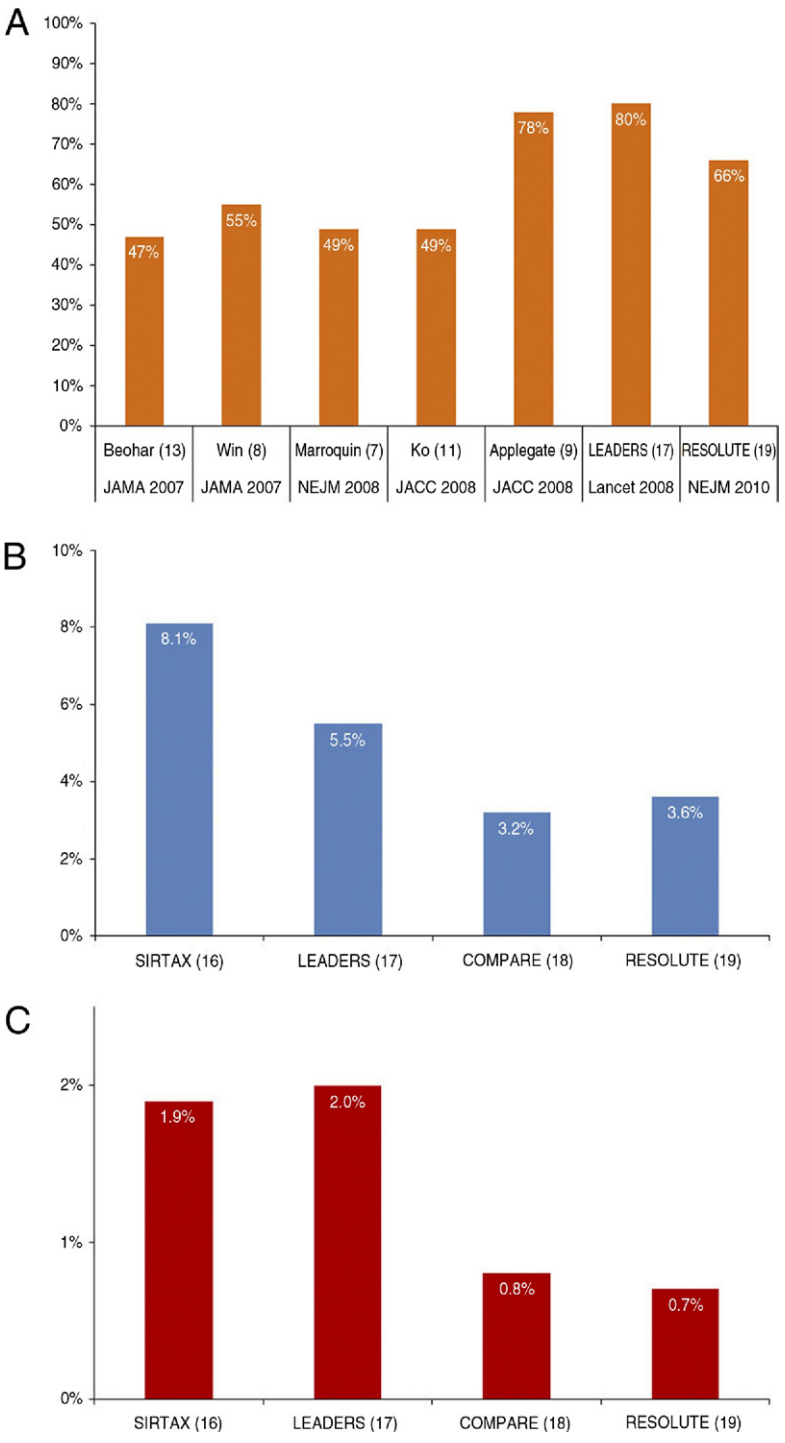

Figure 4 **Results in Perspective**

(A) Frequency of drug-eluting stents implantation among patients with at least 1 off-label characteristic in published reports. **(B)** Rate of clinically driven target lesion revascularization at 12 months with drug-eluting stents in published all comers randomized clinical trials. The rate of protocol-mandated angiographic follow-up differed somewhat between the studies and were as follows: SIRTAX (Sirolimus-Eluting and Paclitaxel-Eluting Stents for Coronary Revascularization): 53%; LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating): 20%; COMPARE (A Randomized Controlled Trial of Everolimus-eluting Stents and Paclitaxel-eluting Stents for Coronary Revascularization in Daily Practice): no angiographic follow-up; and RESOLUTE (A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention): 12%. **(C)** Rate of definite stent thrombosis at 12 months with drug-eluting stents in published all-comers randomized clinical trials.

and EES-treated patients, minimizing the risk of selection bias. Moreover, the clinical findings are buttressed by consistent observations among patients undergoing angiographic follow-up. Therefore, we consider it unlikely that the results would change in larger patient cohorts. Another limitation is the varying degree of patient and lesion complexity within the complex cohort. Thus, patients undergoing multivessel PCI in the setting of an acute MI and reduced left ventricular function were represented in the same group as a patient undergoing PCI of a single long lesion. However, individual clinical and angiographic characteristics defining the complex cohort of the present study have all been shown to portend a worse prognosis, and pooling of all patients in a single cohort provides improved statistical power to detect differences between the 2 devices. The data provided in this report are limited to 1 year, and therefore the present study cannot address the issue of very late ST—the principal shortcoming of the unrestricted use of early-generation DES. Annual follow-up to 5 years, as specified in the protocol, will address this concern in future investigations. Finally, differences in ST between ZES and EES emerged in the overall population but were diminished in the stratified analysis of complex and simple patients. We cannot exclude potential differences between the 2 devices with certainty, due to the low event rates. However, the similar outcomes in terms of cardiac death and MI call into question the relative importance of ST as an isolated event with the use of newer-generation DES.

Conclusions

In this all-comers randomized clinical trial, major adverse cardiovascular events were more frequent among complex than simple patients. The newer-generation ZES and EES were shown to be safe and effective, regardless of complexity, with similar clinical and angiographic outcomes for both stent types through 1 year.

Reprint requests and correspondence: Dr. Stephan Windecker, Department of Cardiology, Swiss Cardiovascular Center Bern, Bern University Hospital, Freiburgstrasse, 3010 Bern, Switzerland. E-mail: stephan.windecker@insel.ch.

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